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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/403,440	01/19/2000	DAVID PHILIP LANE	39749-0001APC	7276

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EXAMINER	
DAVIS, MINH TAM B	

ART UNIT	PAPER NUMBER
1642	

MAIL DATE	DELIVERY MODE
09/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/403,440	LANE, DAVID PHILIP	
	Examiner	Art Unit	
	MINH-TAM DAVIS	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *17 July 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2 and 8* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 8* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/17/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 07/17/07 has been entered.

Accordingly, claims 1, 2, 8 are being examined.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-2, 8 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Bottger et al, 1996 (Oncogene, 13: 2141-2147), in view of McCann A H et al, 1995 (British J Cancer, 71(5): 981-5), and further in view of Lee JM et al, 1995 (Cancer and metastasis Review, 14(2): 149-161) for reasons already of record in paper of 12/13/06.

In the response of 07/17/07, the Declaration of Professor Karen Vousden was submitted. The response recites Crook et a, 1991; Scheffner et al, 1991; Crook et al.,1992; Leach et al., 1993; Oliner et al, 1992; Jones et al., 1995; and Montes de Oca Luna et al., 1995.

The response asserts that not only does the prior art not teach desirability to combine the cited references, it actually provides a strong motivation not the combine the references in the way the Examiner appears to have arrived the combination underlying the present rejection. The response asserts that as supported by the enclosed Declaration of Professor Karen Vousden , it was understood at the priority date of the present application that inhibition of p53 function is important for the development of many cancers, and that this might be the consequence of a number of different events such as (but not limited to):

1. Mutation within the p53 gene.

2. Over-expression of Mdm3 - a known negative regulator of p53 (The Examiner takes note that Mdm3 seems to be a typographic error. As shown in the Declaration, it would be over-expression of **Mdm2**. Mdm3 was not mentioned in the Declaration, nor known in the art at the time the invention was made as over-expressed in cancer and being a negative regulator of p53).

3. Expression of the human papilloma virus E6 protein.

The response asserts that there was evidence that these alterations are mostly mutually exclusive, as shown by Crook et a, 1991; Scheffner et al, 1991; Crook et al.,1992; Leach et al., 1993; Oliner et al, 1992. The response asserts that in other words, tumors with E6 or Mdm2 over-expression do not have mutated p53 and vice versa, and that it is only necessary to inactivate p53 through one mechanism.

The response asserts that Jones et al., 1995; and Montes de Oca Luna et al., 1995 show that the deletion of Mdm2 in mice causes embryonic lethality owing to the activation of p53. The response asserts that accordingly, the person of ordinary skill in the art was taught that inhibition

of Mdm2 can cause activation of p53 in cells where Mdm2 levels are normal (i. e., not over-expressed) but that this was very deleterious to normal tissue.

The response asserts that it was assumed at the time the invention was made that in tumors with no over- expression of Mdm2, p53 was inhibited through other, unknown mechanisms. The response asserts that consequently, it was not known at the time whether inhibition of Mdm2:p53 interaction in such tumors would be an effective therapy, and indeed, there was evidence that such an approach could be very deleterious to normal tissues, which would have advised against even trying this approach. The response concludes that accordingly, the person of ordinary skill in the art is strongly taught against considering the inhibition of Mdm2/p53 in cancer cells that expressed Mdm2 at normal levels as a possible therapy, such a therapy could well be non- specifically toxic and consequently would not be a good approach for tumors without Mdm2 over-expression.

The submission of the Declaration of Professor Karen Vousden and the recitation of Crook et a, 1991; Scheffner et al, 1991; Crook et al.,1992; Leach et al., 1993; Oliner et al, 1992; Jones et al., 1995; and Montes de Oca Luna et al., 1995.

The response has been considered but is not found to be persuasive for the following reasons:

McCann et al teach that in **most** breast cancer patients, **no mdm2** amplification or **overexpression** is detected, and that in mdm2+ breast cancer patients (or type 2 mdm2, where there is 10-50% expression of mdm2) (p.983, first column, first paragraph), the mdm2 protein is associated with low p53 in breast cancer (abstract, lines 7-9, p.983, first column, last paragraph, last 7 lines, tables I-III on page 983). In table II, item under **non-amplified** mdm2, the mdm2

expression is associated with type I p53, i.e. less than 10% p53, or negative p53. Thus, similar to a few breast cancer cases where mdm2 is amplified (table II, item under amplified), the expression of mdm2 in the commonly non-amplified mdm2 breast cancer is **also associated** with **low** expression of p53. This is further confirmed in table III, for mdm2 type 2 in which there is 10-50% mdm2 expression, there is only 1 patient having type 2 and type 3 p53, i.e. those where there is 10-50% or more than 50% of p53, whereas there are 6 patients having low p53, i.e. type 1 p53, in which there is less than 10% p53. It is noted that type 3 mdm2, in which there is more than 50% mdm2, does not even exists in breast cancer patients (table I). It is further noted that in Table III, the column under p53 nuclear accumulation, as 1) type 2 and 3, 2) type 1 and 3) negative is for p53 data, reading horizontally across the table, and the data for mdm2 is read vertically for different types of mdm2.

McCann et al further teach that in familial breast cancer patients, **lack** of **p53 mutation** was reported, thus p53 mutation may not contribute hereditary breast cancer (p.984, first column, first paragraph). McCann et al teach that alterations in Mdm2 and p53 may represent alternative pathway in tumorigenesis, but they are not mutually exclusive in all cases (abstract, last two lines).

Although at the time the invention was made, in the specific breast cancer with no over-expression of Mdm2, the mechanism of p53 inhibition was unknown, however, in view that similar to those few breast cancer having overexpressed mdm2, the presence of mdm2 in most breast cancer which have no over- expression of Mdm2 is also associated with low level of p53, as taught by McCann et al, and in view that mdm2 is a known negative regulator of p53, one would have been motivated to enhance the expression of p53, by disrupting the binding of mdm2

to p53. Further, one would have been motivated to enhance the expression of p53, by disrupting the binding of mdm2 to p53, because: 1) Bottger et al teach that the peptide represents a clear route towards the design of small synthetic molecules that will restore p53 function in human tumors (p.2141, second column, first paragraph), in view that mdm2 binds to p53 and inactivates its function as a transcriptional factor (p.2141, first column), and 2) Lee et al teach that loss of p53 function is correlated with resistance to chemotherapeutic agent.

Further, concerning the response assertion that there was evidence that such inhibition of mdm2 interaction with p53 could be very deleterious to normal tissues, which would have advised against even trying this approach, it is noted that the claims are drawn to ***in vitro*** method for disrupting the binding of p53 and mdm2 in cancer cells, and thus Applicant argues limitation not in the claims.

The response asserts that the Examiner incorrectly interpretes the teaching of McCann et al. The response asserts that McCann et al. teach that although most breast cancers do not over-express Mdm2, a few of them do show elevated Mdm2 expression, and these tumors are significantly associated with low (i.e., wild-type) p53 levels. McCann et al. state that "at the protein level, MDM2 turnouts were significantly associated with tumours having low levels of p53 staining. " (Summary, lines 7-8). This means that those few breast cancers that over-express Mdm2 tend to show low levels of p53 - indicating a retention of wild-type p53. It is therefore that the person skilled in the art would, on the basis of the McCann et al. disclosure, assume the

inhibition of p53 :Mdm2 binding to be an effective therapy in only a few (7%) cases of breast cancer, i.e., those cases which showed over-expression of Mdm2.

The response has been considered but is not found to be persuasive for the following reasons:

The teaching of McCann et al has been set forth above.

Based on the data on tables I-III, the language "at the protein level, MDM2 tumors were significantly associated with tumors having low levels of p53 staining" (Summary, lines 7-8) indicates that not only those few breast cancers that over-express Mdm2 tend to show low levels of p53, but those that do not over-express mdm2 also show low levels of p53, supra. Thus, in view that similar to those few breast cancer having overexpressed mdm2, the presence of mdm2 in most breast cancer which have no over- expression of Mdm2 is also associated with low level of p53, as taught by McCann et al, and in view that mdm2 is a known negative regulator of p53, one would have been motivated to enhance the expression of p53, by disrupt the binding of mdm2 to p53, supra.

The response asserts that the results are surprising, given the understanding of the mechanism involved in p53.

The response has been considered but is not found to be persuasive for the following reasons:

The results from the instant invention are not a surprise.

Given that:

1) p53 is known to be negatively regulated by mdm2, as taught by Bottger et al, and familial breast cancers do not have p53 mutation, as taught by McCann et al,

2) low p53 is correlated with the expression of mdm2 in breast cancer, wherein most of said breast cancer do not over-express mdm2, as taught by McCann et al, and

3) Bottger et al teach that a modified p53 peptide, comprising the 12 amino acids **MPRFMDYWEGLN,** having the consensus sequence **PXFXDYWXXL,** which is the same as the 12 amino acid peptide **MPRFMDYWEGLN** from the 19 amino acid, modified p53 sequence of the claimed invention, is effective in displacing mdm2 from p53,

one would have a reasonable expectation of success that a modified p53 sequence of less than 25 amino acids in length and comprising the 12 amino acids MPRFMDYWEGLN or the consensus sequence PXFXDYWXXL taught by Bottger et al would disrupt the binding of p53 and mdm2 in breast cancer cells in vitro. Further, one would have been expected that the peptide does not inhibit the DNA specific binding property of p53, because the peptide taught by the combined art would disrupt the binding of p53 to mdm2 by binding **only** at the specific p53 binding site for mdm2, as taught by Bottger et al, which is different from the DNA binding site of p53. Moreover, one would have expected that that p53 is activated for DNA specific binding and transcription, because the activity of p53 is to function as a transcriptional factor, via binding to specific DNA , as taught by Lee et al and Bottger et al.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MINH-TAM DAVIS whose telephone number is 571-272-0830. The examiner can normally be reached on 9:00 AM-5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, SHANON FOLEY can be reached on 571-272-0898. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

MINH TAM DAVIS
August 22, 2007

/Larry R. Helms/

Supervisory Patent Examiner